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<p>(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING PROPYLENE GLYCOL AND/OR POLYETHYLENE GLYCOL AND UREA AS ACTIVE MAIN COMPONENTS AND USE THEREOF</p>		
<p>(57) Abstract</p> <p>Composition active for the treatment of hyperkeratotic skin diseases, seborrheic eczema, dermatomycosis and onychomycosis, thickened skin and chapped skin, containing propylene glycol and/or polyethylene glycol and urea as active main components and optionally other active substances and additives, which composition is characterized in that it contains 40 - 80% by weight propylene glycol and/or polyethylene glycol, 5 - 20% by weight urea and 0 - 55% by weight of other active substances and/or additives; as well as the use thereof.</p>		

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Pharmaceutical compositions containing propylene glycol and/or polyethylene glycol and urea as active main components and use thereof.

The present invention is relating to compositions for the treatment of hyperkeratotic skin diseases, seborrheic eczema (mainly of the scalp), mycosis of the skin and nails as well as thickened and chapped skin (rhagades).

The composition consists of a mixture of propylene glycol (optionally polyethylene glycol) and urea as pharmacologically active main components, optionally in combination with lactic acid for the treatment of nails and skin and with the further addition of glycerol and gel forming agents for the treatment of skin as well as alcohol for the treatment of the scalp.

Propylene glycol is preferably used in concentrations between 40 and 80 percent by weight, urea in concentrations between 5 and 20 percent by weight and lactic acid in amounts up to 20 percent by weight, glycerol up to 10 percent by weight, gel forming agents up to 5 percent by weight as well as alcohol up to 55 percent by weight.

It is previously known that propylene glycol is a favourable solvent and penetration promoting agent for other pharmacologically active substances. It is further a very common solvent and is used in several drugs above all in local preparations. Since propylene glycol is a common solvent it can also be used to dissolve urea (UA-A 3 395 236 and GB-A 2 116 425, DE-B 1911144 and DE-A 2847975 and FI-B 56486). For



this purpose propylene glycol is preferably used in concentrations under 10 %, very occasionally up to 40 %, when e.g. propylene glycol is included in combination with fatty acids and about 0.02 % urea (US-A 3 395 236).

Propylene glycol has also been shown to be effective against one type of yeast fungi, *Pityrosporum orbiculare*, giving a specific skin disease *Pityriasis versicolor*. An aqueous solution of 50 % propylene glycol has been shown to give certain results.

In the present invention, by using propylene glycol in high concentrations (over 40 %), in combination with urea and optionally lactic acid, the unique more potent inherent effects of the combinations are used against mycosis of the nails and dermatophytosis as well as hyperkeratotic skin diseases and seborrheic eczema and also thickened and chapped skin.

Propylene glycol

Propylene glycol is a water soluble, odourless, colourless, atoxic solvent, which is used as vehicle in several local and peroral preparations. The agent is also given in the form of injections. Characterizing features for propylene glycol are i.a. its slightly keratolytic (cornea dissolving) and water binding properties. The agent has also an antimycotic and antibacterial effect, (5, 6, 7, 8, 9, 10).

In some cases a local irritating effect has been reported as a side effect (6) with an increased concentration of the solvent. Also allergic reactions are reported occasionally (10).

The agent is also test-wise used on larger skin areas in connection with yeast fungi infections (*pityriasis versicolor*) with favourable results (7). It is shown to potentiate the

effect of other simultaneously added drugs, (5, 6), in connection with dermatomycosis but separately it has a weaker effect, (6). This applies also when treating nails (11).

The concentration of propylene glycol is, however, low when used in local preparations. Propylene glycol is then included in order to dissolve other substances. The penetration promoting properties thereof are utilised in combination with other potent substances, e.g. steroids. Thus, several steroid preparations for local application contain propylene glycol.

The potent keratolytic and fungicidal properties which, i.a. are characterizing the invention are obtained with propylene glycol in a high concentration of about 70 % :

- a) in combination with urea, lactic acid and glycerol as well as gel forming agents for the treatment of hyperkeratotic skin diseases, and
- b) in combination with urea and lactic acid for the treatment of mycosis of the nails.

Thus, propylene glycol is included in the claimed preparation as active substance in combination with other active substances (e.g. urea, lactic acid) and not only as a solvent thereof.

Urea

Urea is a reliable atoxic water soluble substance for the treatment of skin and scalp. Urea is i.a. included in Calmuril and HTH[®]. The Calmuril solution is registered with the indication seborrheic eczema. Urea has an antibacterial, antimycotic, protein-dissolving, keratolytic, water binding and anti-pruritic effect, (11, 13, 14) and has also penetration promoting properties and a low pH-value (15, 2). Urea in 20 to 40 % has a nail dissolving effect under occlusion, (13, 14). According to the method as hitherto used, the nail is covered with a paste of urea under occlusion.

during one week. (13). Said method requires a skilled staff. Side effects reported from the use of urea are i.a. a temporary stinging effect.

Urea may also be included in combination with substances with an antimycotic effect. An antimycotic agent (bifonazol) Mycosporan[®] is presently tested in combination with urea for the treatment of mycosis of the nails (Dermatologica 169; suppl. 1, pp. 117-120 (1984)).

Acidum lacticum (lactic acid)

Lactic acid has i.a. an acidifying effect.

Example

Preparation

I. Urea	20 %
Lactic acid	10 %
Propylene glycol	70 %

II. Urea	20 %
Propylene glycol	80 %

Preparation

III. Urea	20 %
Propylene glycol	40 %
Alcohol (70 %)	40 %

IV. Urea	20 %
Propylene glycol	40 %
Lactic acid	10 %
Alcohol (70 %)	30 %

Control treatment:

Lactic acid	10 %
Propylene glycol	90 %

Preparation *)

V. Urea	15 %
Lactic acid	10 %
Glycerol	5 %
Propylene glycol	70 %

Preparations I and II were used for the treatment of mycosis of the nails, preparation III and IV for the treatment of seborrheic eczema on the scalp and preparation V for treatment of the skin.

The mutual proportional ratios between the substances as stated above are not absolute but can be varied within the limits as stated in the claims and the preparations can be used without limitation for all of the indications as stated even if the test is performed on specific indications.

*) To the preparation for skin treatment a gel forming agent was added in an amount of 0.5-5, preferably 0.5-3 % by weight, in order to obtain a better consistency. E.g. klucel, Carbomer 940 or Macrogol 6000 or optionally other gel forming agents can be used.

A composition containing urea and propylene glycol for the treatment of nail fungus.

Mycosis of the nails is a common complaint, which gives stained, sometimes thickened fragmented nails. Nails can be infected by dermatophytes, yeast fungi, mould, but also bacteria may be contributory (1).

Preparations recorded for the treatment of mycosis of the nails by local application are imidazole derivatives, e.g. Canesten[®], Pevaryl[®], Daktar[®] and previously also a combination preparation Onycho-Phytex, which, however, has a comparatively bad healing effect.

The percentage of healing as obtained by a griseofulvin (Fulcin[®]) is low despite a long time of treatment (2). Further, the agent is only effective against dermatophytes and it lacks effect against yeasts, mould and bacteria.

Neither is the currently registered drug ketaconazole (Fungoral[®]) suitable for the treatment of mycosis of the nails separately due to the side effects of the preparation.

It is a well known fact that mycosis of the nails and especially toe nails as attacked are more difficult to treat than many other forms of mycotic infections. Inferior results are, as mentioned, obtained by local as well as peroral treatment. The period of treatment is calculated to be between 6 and 12 months. Local preparations for mycosis of the nails is furthermore badly documented. Doctors currently advise patients to refrain from treatment of toe nails due to the bad results of treatment.

Review of clinical investigations

The investigation was performed double blind after randomising by comparison of two solutions, one containing a combination of 20 % urea, 10 % lactic acid and 70 % propylene glycol (solution A) (example I) and the other containing propylene glycol 90 % in combination with lactic acid 10 % (solution B) (control).

Urea is well soluble at a concentration of 10-20 % in propylene glycol. By the addition of lactic acid an increased acidity is obtained, which is favourable since a low pH-value inhibits the growth of the fungi in the nail.

Liquid preparations were added in the form of drops and penetrated in that form into the nail substance. The treatment was cosmetically well accepted.

The low effect of many now recorded nail treatment agents probably is due to that the substances do not effectively penetrate the nail attacked by fungi. An increased penetration of the nail substance is obtained by the new composition of urea, propylene glycol and lactic acid. The antimycotic effect might be enhanced by the addition of other pharmacologic active substances.

Twenty-one (21) patients with chronic mycosis of the nails participated in a clinical test. 68 nails infected by fungi were treated (58 toe nails and 10 finger nails). Culturing before the treatment showed in each case growth of *Trichophyton rubrum* attacking the nails.. All of the nails were badly attacked by fungi with thickened nails, discolouration, onycholysis (discharge of the nail plate) and part fragmentation of the nail plate.

The nails were divided into two groups:

Group A obtained solution A (urea, propylene glycol as main substances)

Group B obtained solution B (propylene glycol as main substance).

The duration of the complaint (average value) was 3 years and 10 months (1-10 years).

Treatments were previously performed locally with imidazole-solutions (Pevaryl or Canesten) on average during 6 months (1-24 months). Only 3 of 21 patients stated improved

results, 4 of 21 stated that the nails had become softer, 1 of 21 stated a deterioration and 13 of 21 considered the previous treatment to be without effect. Said patients were, in view thereof, motivated for new treatment.

The nail area as attacked was on average 88 % (group A) and 81 % (group B) respectively, before the treatment with the claimed drug. The solutions were dropwise applied to the nails (2-5 drops per nail) once daily. During the first month the nail plate was also covered with skin tolerant plaster after each application of the nail agent.

Results

The results were documented by photos before and during the treatment (after 14 days and then once per month) and according to record.

Already after 14 days an obvious improvement was recorded. The nail plate was, furthermore, softer in group A (urea-propylene glycol) than in group B (propylene glycol). Parts of the nails as attacked were in group A almost dissolved. The result was recorded as percent of the nail area cured after one and two months respectively (mean values):

	1 month	2 months
Solution A (urea-propylene glycol):	48 %	59%
Solution B (propylene glycol):	22 %	39 %

≥ 80 % of clean nail area was recorded after treatment for two months for 53 % (16 of 30) of the nails in group A and for 26 % (10 of 38) of the nails in group B.

≥ 90 % of clean nail area was recorded after the same treatment period for 30 % (9 of 30) of the nails in group A and for 5 % (2 of 38) of the nails in group B. One nail (group A) was healed altogether during this period.

Thus, urea-propylene glycol gave a significantly better effect than only propylene glycol. The softening effect was, furthermore, more pronounced with urea-propylene glycol.

A follow-up after terminated treatment will be made later on. Since the treatment period for nails is calculated to be at least 6 months, a continued treatment can be expected to give a better treatment result. Complete healing of the nail plate cannot always be expected due to matrix-damage caused by the mycotic infection (14).

Side effects

Two patients recorded a slight stinging effect and tenderness around the nail during one day. Three patients stated a slight redness of the skin around the nail during one to three days. One patient observed also desquamation of the skin around the nail.

Conclusion

By combining 20 % of urea with highly concentrated propylene glycol (70 %) and lactic acid (10 %) a new and previously untested composition for the treatment of onycho mycosis is obtained, which has entailed unexpected and good results. It is further shown that the combination is more effective and has a better softening and more potent keratolytical (cornea disintegrating effect) than propylene glycol alone. By a combination of propylene glycol and urea a penetrating effect furthermore is obtained, which can be promoted by occlusion of skin tolerant plaster around the nail. The combination of propylene glycol and urea is believed to be a solvent which promotes the penetration of other substances having antimycotic effect. As a comparison it can be mentioned that it is commonly known among men skilled in the art, by support of investigations, that preparations solely containing urea have a very low effect on mycosis of the nails.

Nail lesions from other causes

Chronic onychia with impressions in the nail plate can be improved and debris under psoriasis nails can be removed with a solution of urea-propylene glycol at the same concentration (cf. pictures).

Compositions containing urea and propylene glycol with the addition of glycerol and acidum lacticum (lactic acid) for the treatment of skin diseases characterised by hyperkeratosis and scaling

A potent keratolytic and softening effect superior to other commercial preparations or extempore preparations containing e.g. urea or salicylic acid is achieved by a combination of urea with propylene glycol at high concentration. The softening properties are enhanced by the addition of glycerol and lactic acid. The preparation also obstructs the reddening of the skin (e.g. by psoriasis) and has a curative effect also on inflammatory (erythematous) forms of eczema, which seems paradoxical in view of the often irritating effect of propylene glycol at high concentrations. The substances as included are each known and reliable. The novelty lies in 1) the composition of the preparation which gives

- a) an unexpected good effect from the treatment,
- b) pharmaceutical properties where certain particulars concern for the solubility of the substances and so on. Also 2) the indications of the claimed composition are new (cf. the report of the result). The combination of the substances as included should, theoretically, have effect on hyperkeratotic skin diseases and scaling skin diseases by the properties of the substances known per se. However, the rapidly occurring high effect was quite unexpected and might be explained by a synergistic effect between the included substances, said substances being well balanced in relation to each other.

Urea has at a concentration of 10-20 % shown good solubility in propylene glycol. An enhanced acidifying effect, desired in local skin preparations, is obtained by the addition of lactic acid.

Advantages obtained with the claimed preparation in the treatment of hyperkeratotic skin diseases

1. The preparation is cosmetically attractive, since it does not smear or soil, is odourless, penetrates the skin easily and has a low pH-value, which is favourable.
2. The substances as included are acceptable to the skin and give rarely side effects (cf. under the title Side effects).
3. The preparation is an alternative for the patients who desire cortisone-free treatment since the preparation lacks the side effects with i.a. skin atrophy (attenuation) (valid mainly for group III-IV steroids) obtained by cortisone.
4. The preparation is easy to manufacture, the raw materials relatively cheap (cf. under the title Manufacturing process).
5. The preparation is long-lasting without the addition of preservatives (cf. under the title Stability test. Said test is relating to an analysis where the concentration of urea was unchanged after a shelf-life of three months).
6. The preparation has antibacterial and antimycotical properties.
7. Other substances can also be combined with the composition such as e.g. Hydrocortisone, or fluorinated corticosteroides in an amount of up to 2 %, antimycotical substances such as e.g. imidazole derivatives in amounts up to 2 %, collodium 0-10 %, salicylic acid 0-10 %, vitamin A 0-1 %, vitamin A-acid 0-1 % (weight) and derivatives thereof, which

give several advantages i.a. by increasing the penetration properties of the steroid.

8. One advantage with the preparations according to the claims is that in addition to being pharmaceutically active in the amounts as defined in the claims, they also can act as solvents for other pharmaceutically active substances such as e.g. the substances stated above.

A report of the results of treatment of chronic hyperkeratotic skin diseases

Examples of diseases that can be treated are:

- psoriasis
- pustulosis palmoplantaris
- tylotic eczema
- hyperkeratotic eczema
- neurodermatitis
- ichthyosis
- keratoderma
- mycotic infections
- clavi (corns)

In total 40 patients are presently being treated.

Symmetrically located similar skin lesions were chosen for the treatment. One side was treated with the claimed composition consisting of urea-propylene glycol, lactic acid, glycerol and a gel forming agent (example V), and the other side with a potent corticosteroid (group III) and a known softening preparation containing salicylic acid 2-5 % or urea 10 % (control side).

Results

The preliminary results, which were documented by photos, were so favourable that conclusions with respect to the effect of the treatment could be drawn already at an early stage. The effect of the claimed composition was unexpected and in some cases almost dramatical. A potent desquamation of the skin gave in all cases, often already after 14 days, a remarkable improvement and in certain cases a complete cure after a treatment of one month. The effect was more rapid and better than that obtained by the control treatment. The treatment of hyperkeratotic eczema, chronic mycotic infections and psoriasis gave the best results. Said complaints were reported separately. The preparation has also an excellent effect on dry skin and chaps.

Side effects: a slight stinging effect was noted in individual cases.

A. Hyperkeratotic eczema

These are characterized by thickened, scaling skin often with chaps (rhagades). Eczema on the palms of hands and the soles of feet was treated.

Results

Very favourable results with a rapid, one-sided peeling effect and a remarkable improvement in the curing of the eczema were noted for the claimed preparation. Remarkably, also painful, deep rhagades (chaps) were cured and the pain disappeared. The curing period was on average about one month. The control side showed inferior results.

B. Chronic mycotic infections

Mycotic infections caused by a dermatophyte, commonly *Trichophyton rubrum*. The symptoms are often a dry chapping in the palms of the hands and the soles of the feet. The infections are, as a rule, chronic, and therefore difficult to treat and frequently recurrent.

Results

Remarkably good results with rapid desquamation and apparently healed skin after about one months treatment is achieved with the claimed preparation. The combination of rapid repellation of infected skin cells, the antimycotic effect of the preparation as well as its low pH-value probably contribute to the effect. Said three properties are achieved by the well balanced exact composition of the preparation. These properties together make the preparation new in relation to other reliable antimycotical agents. No stinging effect was noted during treatment of the palms of the hands and the soles of the feet, which, however, might be a problem if the agent is used on discharging or reddening skin areas or in groins. Other methods of treatments are presently recommended in this respect. Thus, the main indication for treatment of dermatomycosis is a chronic infection in the palms of the hands and the soles of the feet or dry, scaling mycotic attacks on smooth skin.

Pityriasis versicolor

Caused by a yeast fungus, *Pityrosporon orbiculare*, which also can be treated with the preparation according to the invention. The treatment of said complaint has been tested previously with 50 % propylene glycol in water solution, and thus, is previously known (7).

Conclusion

Novelty: the composition of the claimed preparation with the indication dry eczema and mycotic infections (dermatophytosis). The invention is not obvious in view of the unexpected favourable effect of the product.

C. Psoriasis

Psoriasis is a skin disease, characterized by reddened, flaking skin lesions. The disease has, as a rule, a chronical course. Local agents for the treatment of psoriasis are often smeary and discolouring e.g. dithranol or tar. Steroid preparations are cosmetically attractive but can give the side effects of cortisone in the form of i.a. skin attenuation. Softening preparations containing e.g. salicylic acid and urea in a cream or ointment base have a certain peeling effect but are not separately sufficiently active. A cosmetically acceptable local agent having a more potent effect and lacking the side effects of cortisone for the treatment of psoriasis is presently not available.

Symmetrically situated, well defined chronical psoriasis lesions were chosen for the treatment in order to more critically evaluate the effect of the claimed preparation. One side was treated twice a day with the claimed preparation and the other side obtained common softening treatment and a potent steroid ointment (group III), the last mentioned group twice a day.

Result

The result of the treatment was totally unexpected. A very rapidly occurring effect with a pronounced recovery was noted already after fourteen days of treatment with the claimed preparation. A treatment period of one month resulted in many cases in a complete healing of the area as treated. The effect was comparable, or better than that obtained on the

control side which was treated with a potent (group III) steroid. In addition to a keratolytic effect, it was also noted that the erythema receded. Said anti-psoriatic effect is difficult to explain in the light of the present knowledge about the separate components as included. Said components might have a synergistic effect and might also simultaneously have an anti-inflammatory or anti-mitotic effect.

Side effects

A slight stinging effect was noted in some cases (common for urea). The patient considered the cosmetical properties of the preparation to be very favourable (cf. page 11). The properties of the preparation which bring about rapid desquamation are also very important e.g. in combination with treatment with light.

Conclusion

The indication for said composition is new. The result of the treatment was very favourable with an unexpected, rapid keratolytic and anti-psoriatic effect comparable with potent corticosteroids and more effective than common softening treatment of the type urea in a cream base.

The preparation according to the invention provides a very valuable addition to the treatment armoury for psoriasis patients since it is cosmetically attractive and has a good effect.

Further indications:

seborrheic eczema
verrucae

Seborrheic eczema

Seborrheic eczema is a common complaint with itching, erythema and scaling on the scalp. The eczema is often also located on the face, in the armpits and the groin. The hitherto most common methods of treatment have been different steroid-(cortisone)-preparations which have a symptomatic alleviating effect with a temporary itch-relieving and anti-inflammatory effect.

The etiology of seborrheic eczema is commonly discussed and a relatively new hypothesis is that a yeast fungus (*Pityrosporon ovale/orbiculare*), can be one of the causes thereof (3, 4).

A new method to obtain results of the treatment of seborrheic eczema should be the use of a drug which inhibits the yeast fungus growth and thereby not only gives a symptomatic alleviation but also eliminates the causes thereof. Propylene glycol has such a inhibitory effect.

There is, in view thereof, a common demand for alternative preparations intended for the treatment of seborrheic eczema.

An alternative preparation for the treatment of seborrheic eczema is now obtained by the present invention wherein propylene glycol in mixture with urea is used as active substance, optionally in combination with other active substances.

Some test cases of seborrheic eczema of the scalp treated with the composition III and IV are reported under the title Example.

The treatment is effective, but the symptoms recidivate after about one to two weeks after the end of the treatment. Two courses of treatment per week are often enough for treatment of maintenance. The solution is in these cases washed out after about five to twelve hours. The preparation for the hair can give a somewhat greasy feeling to the hair and scalp, which however, can be an advantage with dry scalps. The preparation according to the invention is an alternative for the patients who wish to avoid steroid treatment (cortisone preparation) for their eczema. No side effects from the preparation are observed.

Verrucae

A certain effect was also obtained where verrucae was treated with the solution used for mycosis of the nails, which solution contained urea, propylene glycol and lactic acid. The difficulty to force the preparation to remain on the verrucae might be eliminated by e.g. collodium.

The claimed preparation, has by its composition, shown unique properties due to its effect on a great number of skin diseases having different etiology. This is very uncommon in medical connection. It has further been shown that the combination (urea-propylene glycol) has a more potent keratolytic (cornea disintegrating effect) than propylene glycol separately. The combination is furthermore, effective for nail mycosis.

The skin preparation has, in addition to keratolytic properties, also an anti-psoriatic effect and in some cases also an anti-inflammatory effect. This is surprising and cannot be explained by the mechanisms as regards the effects of each of the separate substances. The combined treatment has also shown a better effect than preparations only containing urea and in many cases also potent corticosteroids (group III).

Manufacturing example 1:

Urea	20 %
Lactic acid	10 %
Propylene glycol ad.	100 %

Preparation prescriptions:

The urea is dispersed as finely as possible and mixed with a minor amount of propylene glycol. The remainder of the propylene glycol is then added and all of it stirred together until the urea is dissolved (time consuming). Finally, lactic acid is added.

Manufacturing example 2:

Gel forming agent	0.5-	3 %
Glycerol	85 %	5 %
Lactic acid		10 %
Urea		15 %
Propylene glycol ad.		100 %

Preparation prescription:

The urea is dispersed as fine as possible and mixed in a minor amount of propylene glycol, whereafter the remainder of the propylene glycol is added and all of it stirred together until the urea has dissolved (time consuming). The glycerol and the lactic acid is added.

A gel forming agent is mixed into a small amount of the above mentioned solution to a homogeneous mixture, whereafter the remainder of the solvent is added and everything is stirred until a homogeneous gel is formed (time consuming).

Stability Test

A stability test was performed by the Central Laboratory of Apoteksbolaget, Solna, on a preparation with the composition:

20 % urea
70 % propylene glycol
10 % lactic acid

Analysis after three months of three samples of the preparation wherein the amounts of urea, which is the chemically instable composition shall be included in an amount of 18-22 %. The results as obtained:

Vial 1. 20.5 %
" 2. 19.9 %
" 3. 19.9 %

1. Zaias A. Onychomycosis. Arch Derm 1972; 105: 263-74.
2. Ishii M, Hamada I, Asai Y. Treatment of onychomycosis by ODI therapy with 20% urea ointment and 2% tolnaftate ointment. Dermatologica 1983; 167: 273-9.
3. Priestley G C, Savin J A. The microbiology of dandruff. Br J Dermatol 1976; 94: 469-71.
4. Shuster S. The aetiology of dandruff and the mode of action of therapeutic agents. Br J Dermatol 1984; 111: 235-42.
5. Nielsen P G. The importance of the vehicle in the treatment of dermatophytosis in hereditary palmo-plantar keratoderma. Mykosen 1984; 27 (5): 227-30.
6. Gamburg Nielsen P. Dermatophyte infections in hereditary palmo-plantar keratoderma. Dermatologica 1984; 168: 238-41.
7. Faergemann J, Fredriksson I. Propylene glycol in the treatment of tinea versicolor. Acta Derm Venereol 1979; 60: 92-3.
8. Faergemann J, Bernander S. The activity in vitro of five different antimycotics against pityrosporum orbiculare. Acta Derm Venereol 1979; 59: 521-4.
9. Leyden J J, Stewart R, Kligman A M. Updated in vivo methods of evaluating topical antimicrobial agents on human skin. J Invest Dermatol 1979; 72: 165-70.
10. Martindale, The extra pharmacopoeia, Ed. 28, 1982.
11. Bagatell F K. Topical therapy for onychomycosis. Arch Derm 1977; 113: 378.
12. Ashton H, Frenk E, Stevenson C J. Urea as a topical agent. Br J Dermatol 1970; 84: 194-6.
13. Farber E M, South D A. Urea ointment in the nonsurgical avulsion of nail dystrophies. Cutis 1978; 22: 689-92.
14. South D A, Farber E M. Urea ointment in the nonsurgical avulsion of nail dystrophies - a reappraisal. Cutis 1980; 25: 609-12.
15. Volting S. Non-traumatic removal of the nail and simultaneous treatment of onychomycosis. Dermatologica 1984; 169 (suppl 1): 117-20.

Fig. 1 Onycho Mycosis

Onycho mycosis during 3 years. Treatment with imidazole solution during 1 year without effect.

- a) Before treatment with the claimed preparation.
- b) After 14 days of treatment.
- c) After two months of treatment. The new nail has now started to develop proximally (at the top) and the discoloured part is simultaneously successively displaced downwards. This is evident if one compares pictures b and c.

Fig. 2 Onycho Mycosis

Onycho mycosis during about 3 years. Previous treatment with an imidazole solution made the nails somewhat softer but the patient did not notice any improvement.

- a) Before the treatment with the claimed preparation.
- b) After 14 days of treatment.
- c) After one month of treatment.

Fig. 3 Onycho Mycosis

- a) Before treatment with the claimed preparation.
- b) Example of the potent nail disintegrating effect of the preparation after one month.
- c) After two months. The infected nail substance is displaced and a new nail which cannot be reinfected starts to grow.

Fig. 4

Onychia About 3 years damage of the nail plate. The impression has been newly formed as the nail has grown. Probably matrix damage in connection with hand eczema.

- a) Before the treatment with the claimed preparation.
- b) Treatment results after 1.5 months.
- c) Treatment results after 2.5 months.

Fig. 5Toxic traumatic iterative hand eczema

Hand eczema since 1969.

Hand eczema before the treatment. The claimed preparation was applied to the right hand. (Marked with H).

A potent steroid cream (group III) Celestona valerat was applied to the left hand. The hand eczema was somewhat more pronounced on the right hand from the beginning.

- a) The result after 14 days of treatment with the claimed preparation. (Right hands (Hö) bottom pictures).
- b) The result after 14 days of treatment with a potent corticosteroid (group III) Celastona valerat. (Left hand bottom picture.)

Fig. 6Tyloitic eczema

Chronical eczema in both palms of the hands. Heredity of psoriasis.

- a) The right hand (marked with H) was treated with the claimed preparation. The left hand was treated with a potent corticosteroid in combination with salicylic acid (Diprosalic ointment).
- b) The treatment results after one month. Somewhat better results in the right hand palm after treatment.

Fig. 7Nickel eczema, psoriasis, Hyperkeratosis, Rhagades

- a) A woman with chronic nickel eczema and psoriasis since several years ago. Thick hyperkeratosis with rhagades in both soles of the feet. Worse at the right side, more pain when walking. The right foot was treated with the claimed preparation, the left foot was simultaneously treated with a potent steroid ointment (group III) Betnovat in combination with salicylic Essex cream. (The right side marked with H).

- b) The results after hardly one month of treatment.
- c) The result after slightly more than two months of treatment. The right side is remarkably better. Only a fold of the skin now remains of the deep, painful chapped formation. The pain has disappeared from the right foot.

Fig. 8

Psoriasis

A patient with psoriasis since 1967.

The right side (marked with H) is treated with the claimed preparation. The left hand side (not marked) was treated with a potent steroid ointment (group III) in combination with salicylic (Diprosalic). In combination, a further keratolytic treatment on the left hand side with salicylic Diachylon 5 %.

- a) The results after 14 days of treatment with the claimed preparation. The skin in the centre is healed.
- b) The results after 14 days of treatment with Diprosalic and salicylic Diachylon.

Fig. 9

Tinea Man (fungus infection)

A chronic fungus infection in the palm of the right hand caused by *Trichophyton rubrum*.

The result after one month of treatment.

The palm of the right hand was healed at that time.

CLAIMS

1. A composition active for the treatment of hyperkeratotic skin diseases, seborrheic eczema, dermatomycosis and onychomycosis, thickened and chapped skin, comprising propylene glycol and/or polyethylene glycol and urea as active main components, and optionally other active substances and additives,

c h a r a c t e r i z e d in that the composition contains

40 - 80 % by weight of propylene glycol and/or
polyethylene glycol

5 - 20 % by weight of urea and

0 - 55 % by weight of other active substances and/or
additives.

2. A composition according to claim 1, c h a r a c t e r -
i z e d in that it contains:

50 - 80 % by weight of propylene glycol and/or
polyethylene glycol;

5 - 20 % by weight of urea and

0. - 45 % by weight of other active substances and/or
additives.

3. A composition according to claim 1 or 2, c h a r a c t -
e r i z e d in that the further active substances and
additives are

0 - 10 % by weight of glycerol

0 - 5 % by weight of gel forming agent

0 - 20 % by weight of lactic acid

0 - 55 % by weight of C₁₋₄-alcohols

0 - 2 % by weight of glucocorticoids such as
hydrocortison or fluorinated corticosteroids

0 - 2 % by weight of antimycotic substances such as
imidazole derivatives

0 - 10 % by weight of collodium
0 - 10 % by weight of salicylic acid
0 - 1 % by weight of vitamin A
0 - 1 % by weight of vitamin A acid or derivatives thereof.

4. A composition according to any of claims 1 and 3, characterized in that the further active substance is 10 % by weight of lactic acid.

5. A composition according to any of claims 1 and 3, characterized in that the further additive is 30 - 40 % by weight of ethanol.

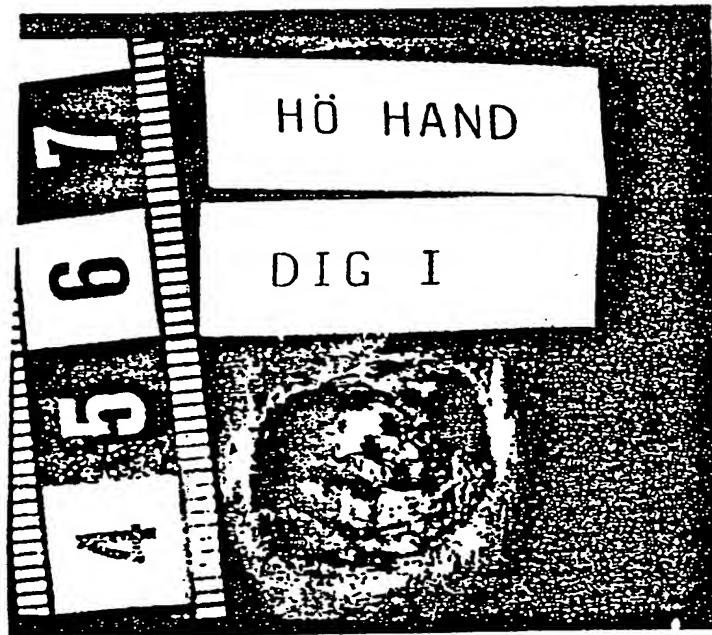
6. A composition according to claim 1 to be used as penetration promoting solvent for glucocorticoids or antimycotic substances.

7. A composition according to any of examples 1-V.

8. A composition according to claim 1, in the form of a solvent, gel, ointment or cream, preferably in the form of a solvent or a gel.

9. The use of the composition according to claim 1 for the treatment of hyperkeratotic skin diseases, seborrheic eczema preferably of the scalp, dermatomycosis and onychomycosis, thickened skin and chapped skin (rhagades).

10. The use of the composition according to claim 2 for the treatment of hyperkeratotic skin diseases, preferably psoriasis.



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a

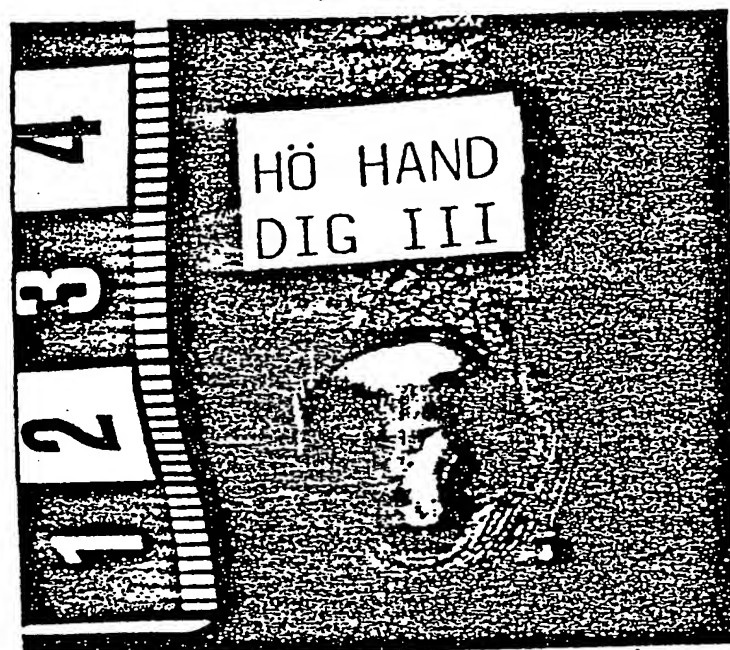


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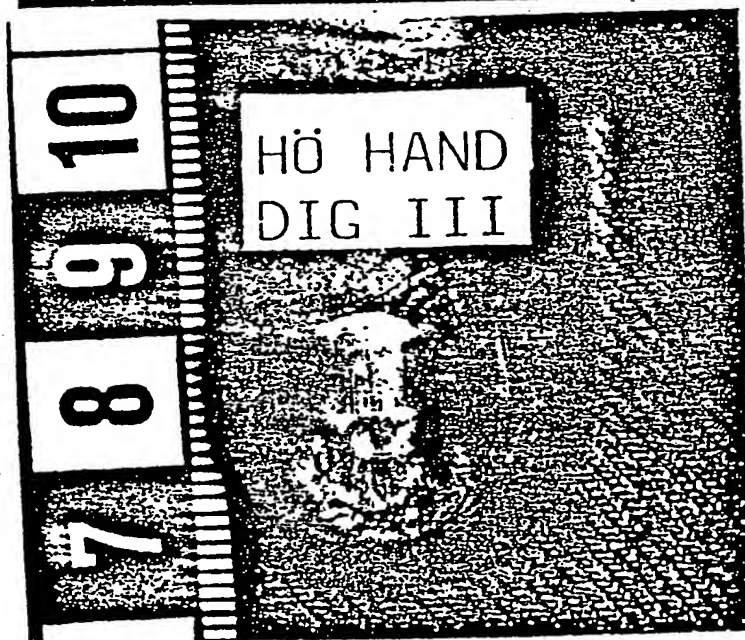
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Fig 2



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a



b



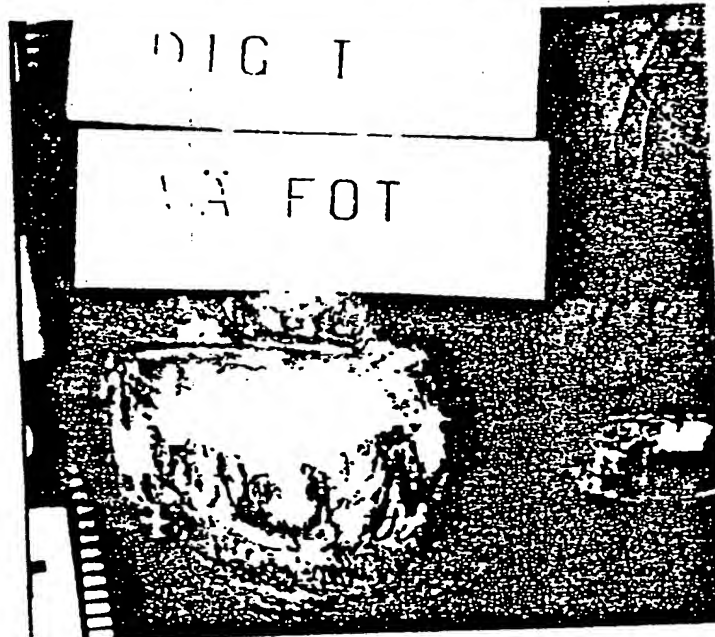
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Fig. 3



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a



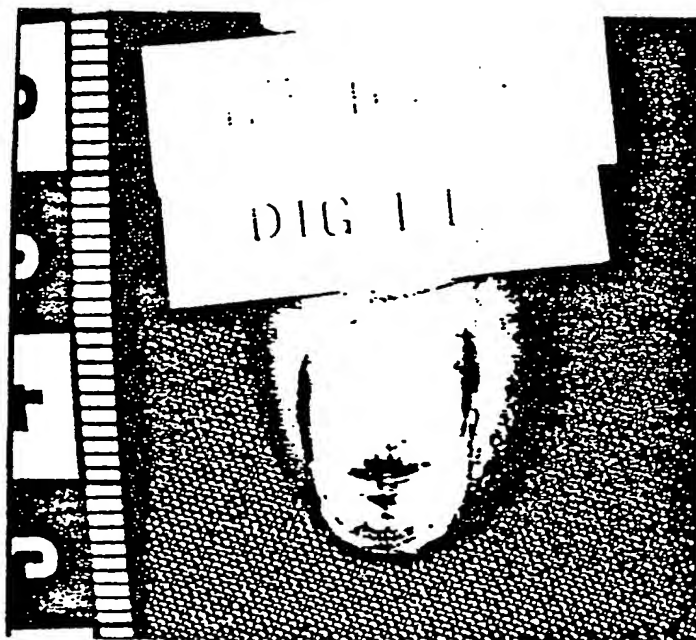
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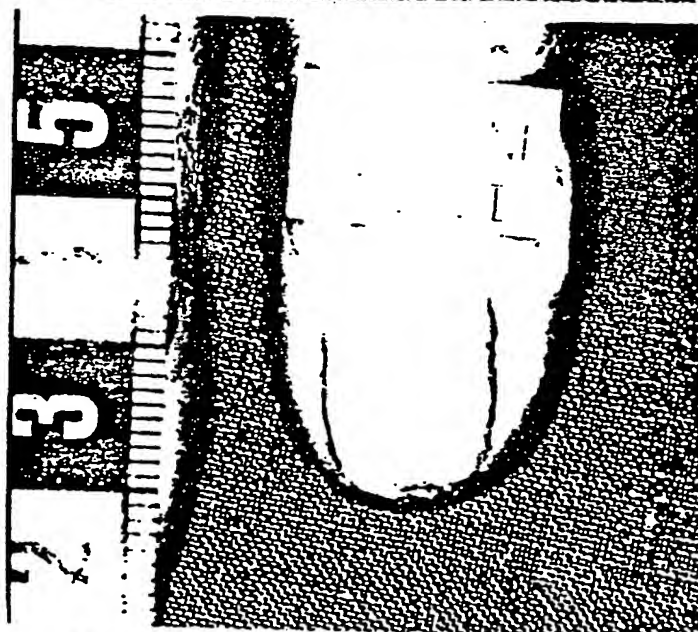
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Fig. 4

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a



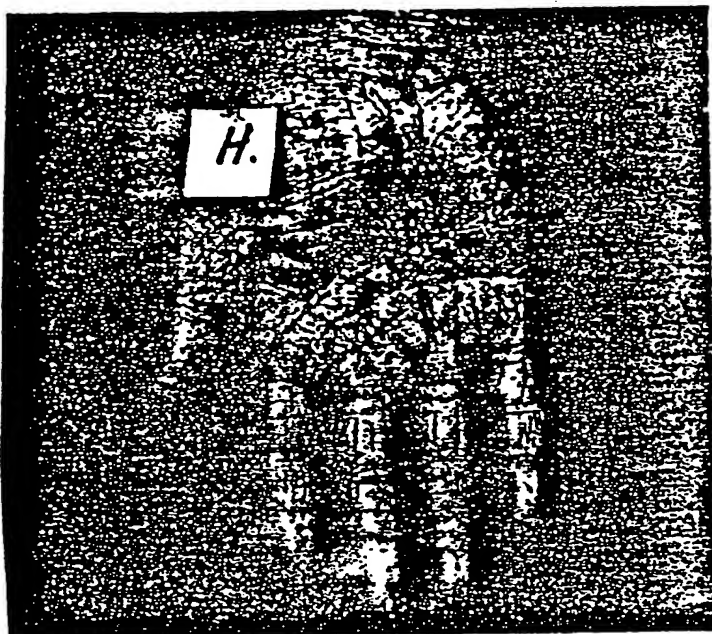
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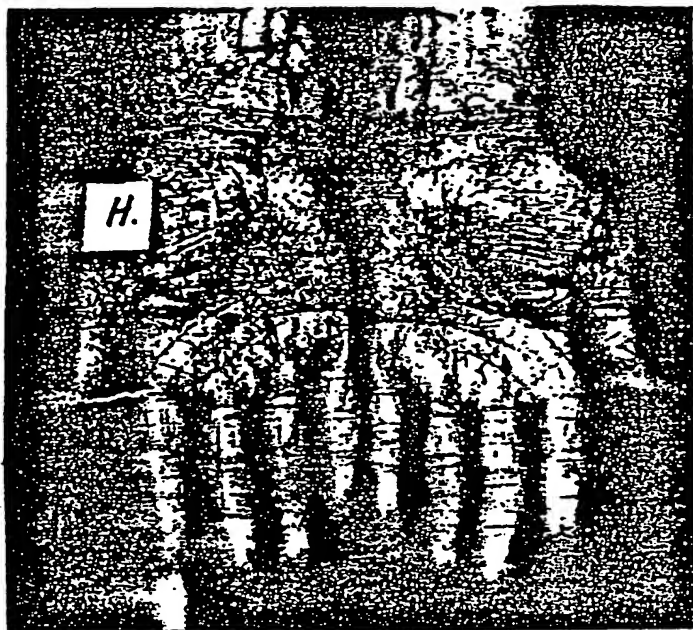
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Fig 5

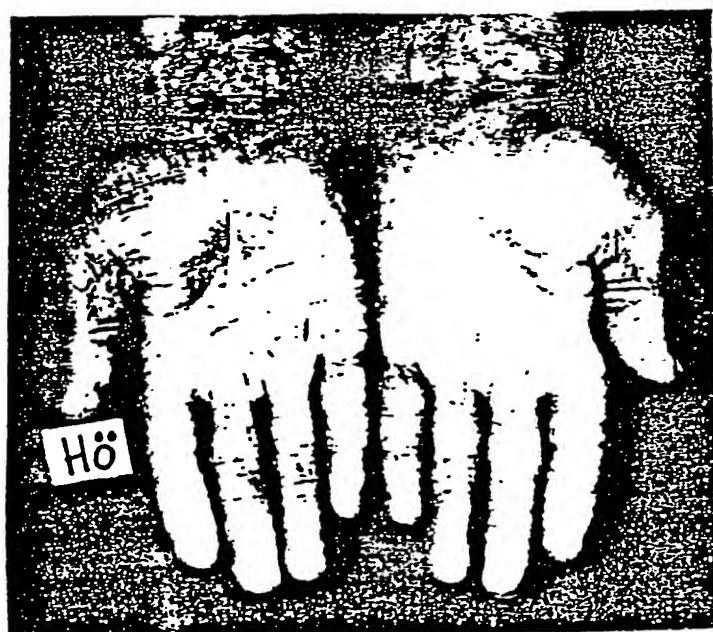
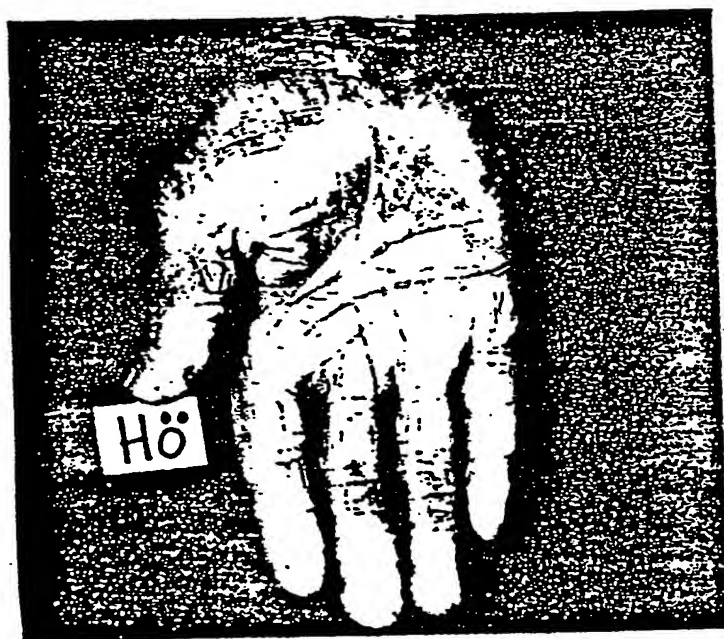
5/9



a



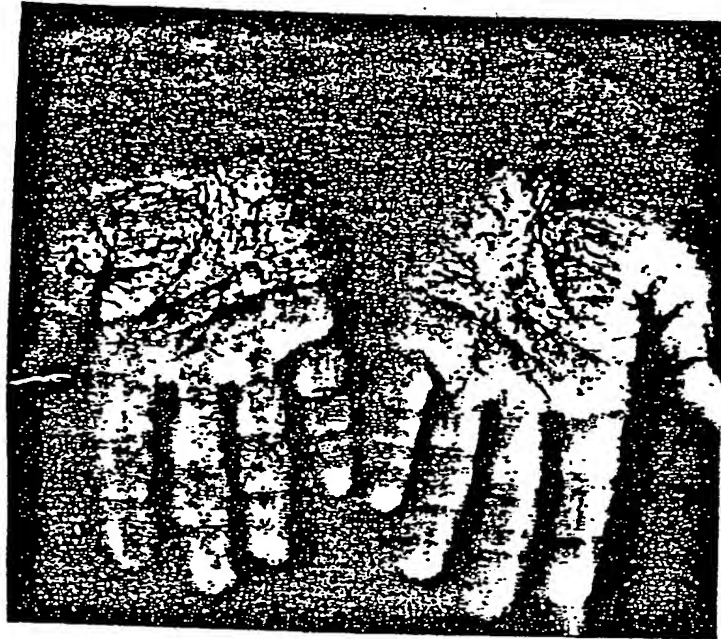
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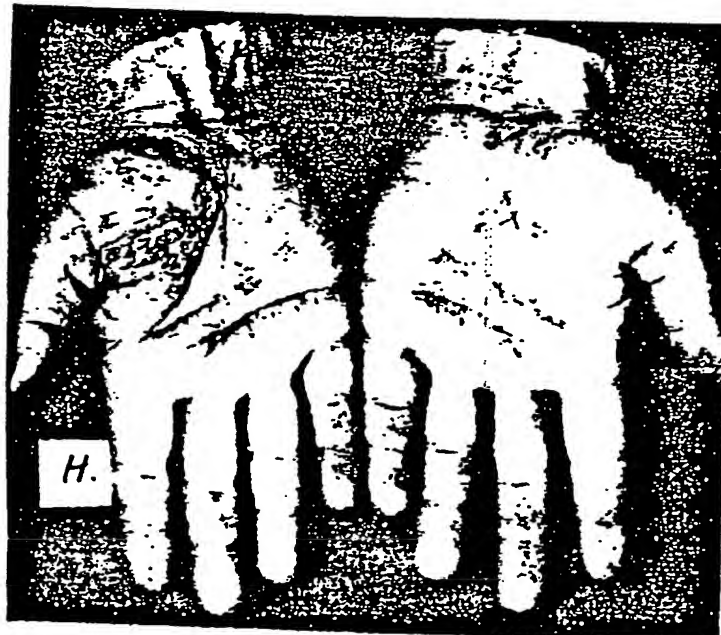
SUBSTITUTE SHEET

Fig. 6

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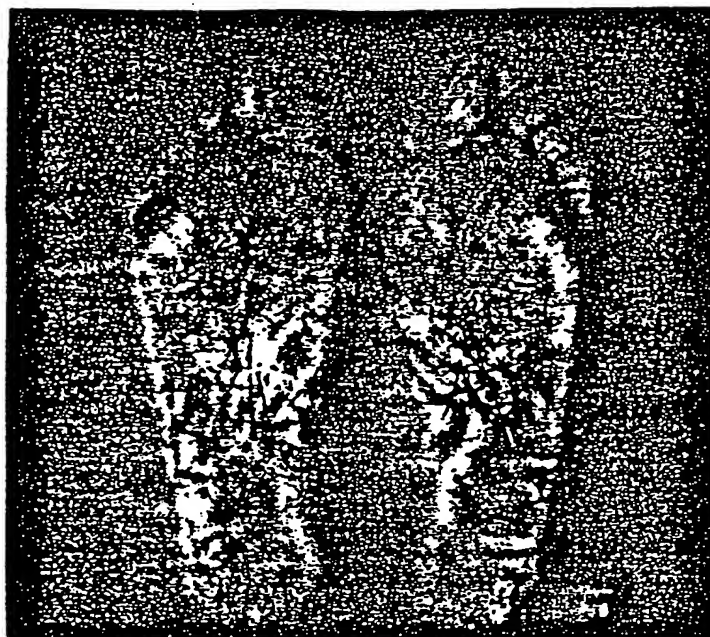
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b

Fig 7

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a



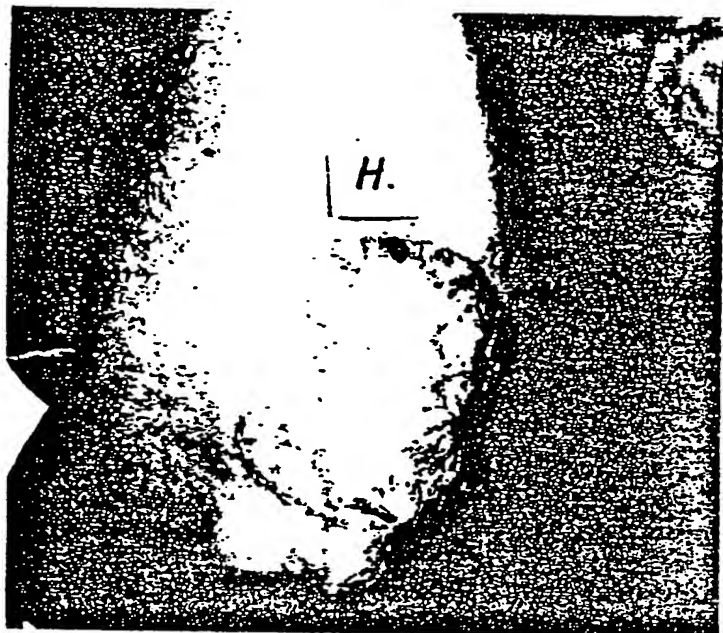
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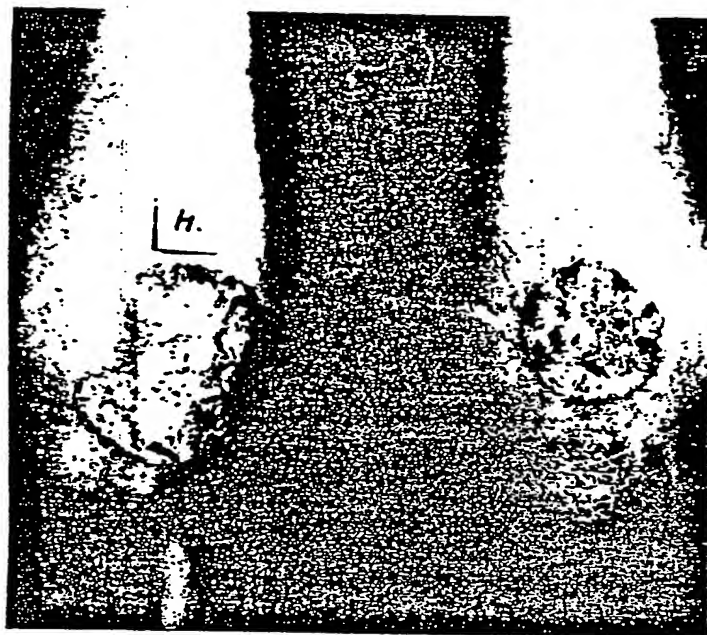
c

Fig. 8

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a



b

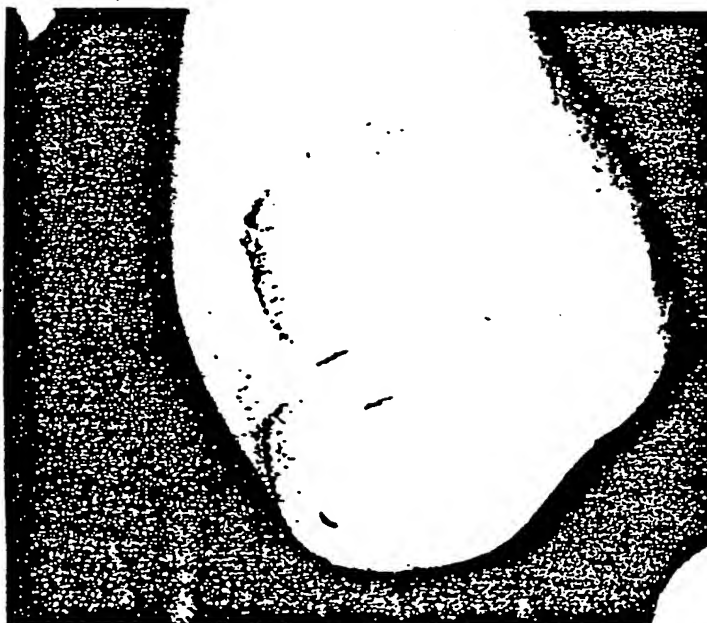
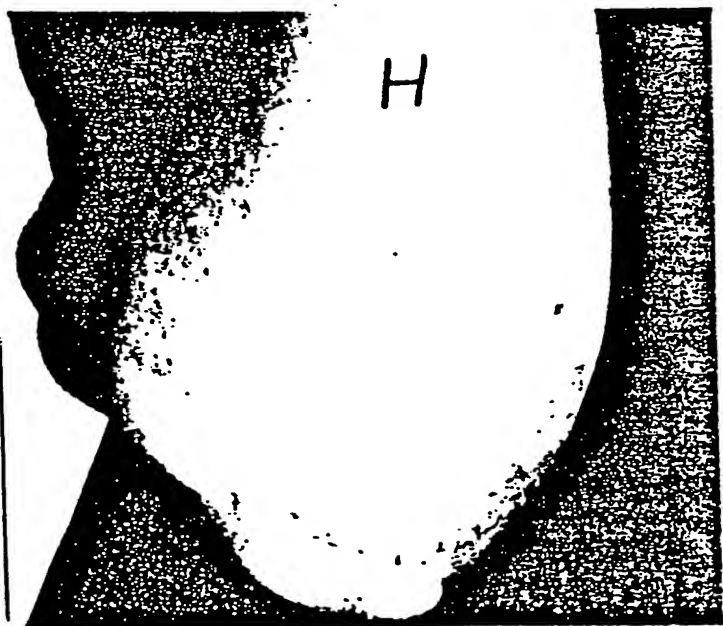
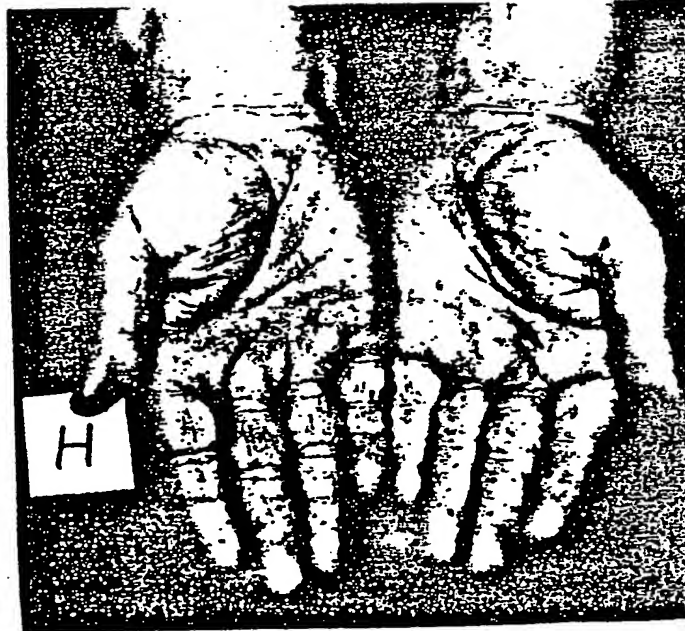
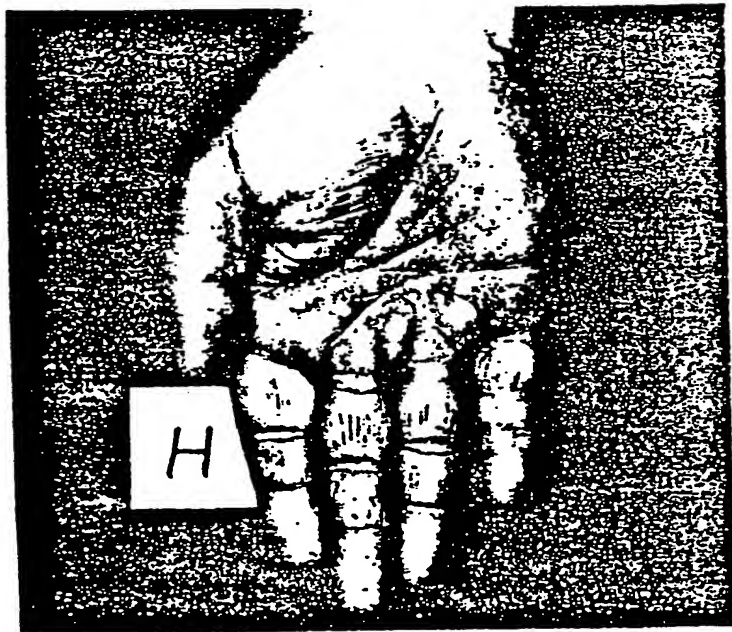
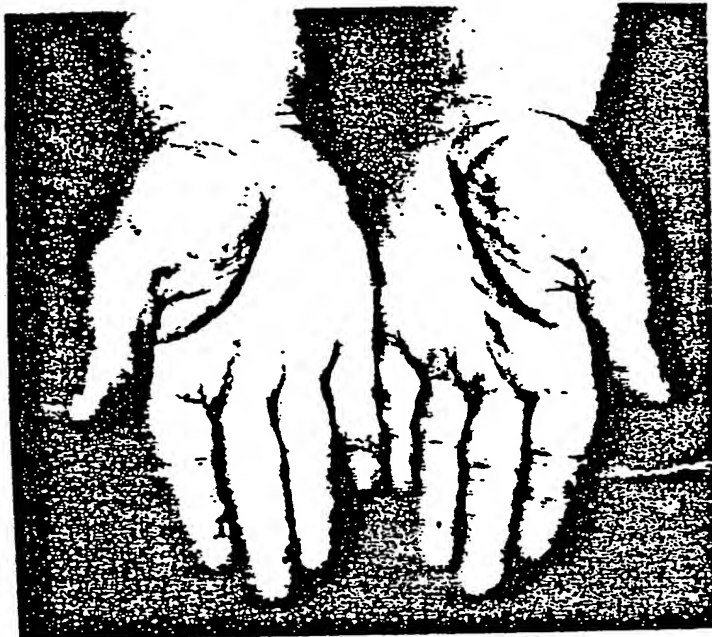
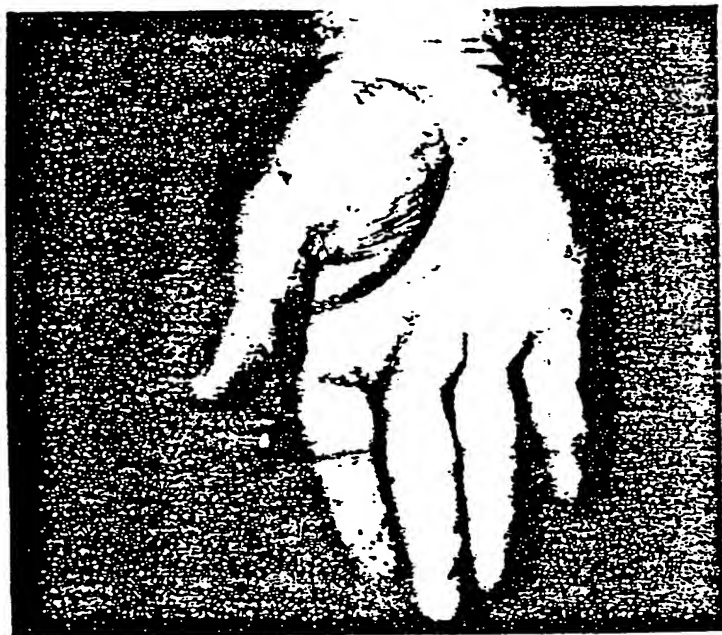


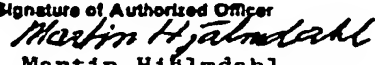
Fig. 9

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INTERNATIONAL SEARCH REPORT

International Application No PCT/SE87/00053

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC ⁴		
A 61 K 31/17, 31/045, 31/765, 7/04, 7/48, 47/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
IPC 2,3,4	A 61 K 7/04, /48, 31/045, /17, /19, /565, /57, /765, /77, ⁴ 7/00	
IPC 1	A 61 k 27/00	
US C1	424: 322, 343, 360, 366; 514: 557, 588, 724, 738	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
SE, NO, DK, FI classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	DE, B, 1 911 144 (MEDISAN AB) 17 September 1970 see especially column 2, lines 10-24, column 4, lines 6-10, and example 5 & NL, 6903383 LU, 58143 FR, 2003312 GB, 1232569 CH, 513648 US, 3666863 BE, 729465 AT, 306928 CH, 576789 AT, 294319	1-8
Y	DE, B, 2 608 221 (BEIERSDORF AG) 21 July 1977 see especially column 1, lines 23-39, column 5, line 18- column 6, line 2, and example 1 .../...	1-8
<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
1987-04-16	1987-04-23	
International Searching Authority	Signature of Authorized Officer	
Swedish Patent Office	 Martin Hjalmdahl	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 9-10, because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by
therapy [PCT Rule 39 (i v)]

2. ☒ Claim numbers 6, because ^{it} ~~they~~ ^s ~~relate to~~ parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The expression "antimycotic substances" in this claim is
too broad and lacks differentiating power.

The search on claim 6 has therefore been incomplete.

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	BE, 851922 LU, 76850 NL, 7702002 FR, 2342059 AT, 346495 JP, 1941877 JP, 52105225 CH, 627645 SE, 7702170	
X,Y	EP, A2, 0 138 029 (TAKEDA CHEMICAL INDUSTRIES) 24 April 1985 see especially page 4, lines 14-27, page 6, lines 1-14, and Formulation Example 1 & JP, 60056921 JP, 61036219	1-8
Y	GB, A, 2 086 223 (R EDWARDS) 12 May 1982 & US, 4239781 US, 4361585 FR, 2491760 DE, 3038604	1-8
Y	GB, A, 2 116 425 (ROHM PHARMA GmbH) 28 September 1983 see especially 5th example & FR, 2523447 DE, 3210138 JP, 58167508	1-8
Y	US, A, 3 395 236 (C J WHITE) 30 July 1968 see especially column 1, lines 15-45 and example 2	1-8
Y	Patent Abstracts of Japan, abstract of JP Kokai No 52-87235, published 20 July 1977	1-8
Y	Dermatologica, Volume 169, Suppl 1, issued 1984 (Basel), S Nolting, "Non-traumatic removal of the nail and simultaneous treatment of onychomycosis" see pages 117-120, especially page 118, right column, third paragraph	1-8
Y	Archives of Dermatology, Volume 113, issued 1977, March (Chicago), F K Bagat ll, "Topical therapy for onychomycosis", see page 378	1-8
 /	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	Kärnan, Volume 9, No 1, issued 1985 (AB Leo, Helsingborg, Sweden), J Faergemann, "Pityriasis versicolor. Orsak, diagnos och behandling", see pages 13-17, especially page 13, left column, third paragraph and page 17, left column, second paragraph	1-8

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